

*A
concern
T1520X*

*20
25. A method as in Claim 19 wherein*

*A is $\text{C}^{\text{H}}\text{...OH}$ or $\text{C}^{\text{OH}}\text{...H}$ and the hydroxy group thereof is
then oxidized to a keto group.*

REMARKS

The specification has been amended to correct typing and transcription errors and to make the English more idiomatic.

Claims 6-25 are in the application. In view of the submission of two further independent claims in excess of the number of independent claims for which a fee has already been tendered, and in further view of the submission of a total of 20 claims, the applicants enclose herewith a check in the amount of \$40.00 in payment of the requisite statutory fee.

NP
In view of the redrafting of the claims as new Claims 6-25, the Examiner is respectfully requested to reconsider his earlier rejection under 35 USC 112 and not to apply the rejection to the claims now in the application.

Thus, for example, the claims no longer read on compounds having a fused pyrazole ring in the 2,3-position of the steroids of interest and compounds in which group R₄ is halogen, amino, substituted amino, or a nitrogen heterocycle are no longer claimed. The compounds which are defined in the new claims do find support in the specification.

As concerns the claimed method, the redrafting of former method Claim 2 as new method Claims 20-25 is believed

to overcome the Examiner's objection of record. Thus, the hydrolysis recited in these claims is now defined as one involving "hydrolyzing with weak acid". Such a proton-catalyzed hydrolysis with a weak or dilute acid is disclosed in the present specification on page 6, line 16 to page 7, line 17.

In all claims, alternative language has been removed and an attempt has been made to simplify the terminology. Thus, the definition of R_4 in original Claim 1 as "straight-chain or branched aliphatic hydrocarbon" has been simply recited in the new claims as "alkyl". This term is synonymous with "aliphatic hydrocarbon" and, evidently, embraces both straight-chain and branched materials. The fact that different substituents may be present in the 11-position, depending on whether there is an unsaturation in the 9, 11-position or not, has been made clearer by the separate showing in each claim of compounds which are either saturated or unsaturated in this position. Further, since the formulas presented in the claims indicate per se the possible presence of additional double bonds in the 1,2-, 2,3-, and 6,7-positions by the presence of dotted lines in the formulas, a further verbal reference to such possible additional double bonds has been omitted from the claims. The meaning of the formulas is fully explained and illustrated in the specification.

In view of the direction of the new claims to 17, 21-dicarbonate esters (and related variants in the 21-position), the Examiner is respectfully requested to

reconsider his rejection under 35 USC 102 based on the Phillipps et al. reference of record and not to apply the reference to the new claims. In view of the exclusion of 21-hydroxy compounds from Claims 6-25, no rejection under 35 USC 102 based on the Phillipps et al. patent will lie.

Further, it is urged that the compounds of the present invention having a substituent other than hydroxy in the 21-position have properties which render them unobvious from the 17-carbonate-21-hydroxy compounds of the Phillipps et al. reference.

More in particular, although the 17-carboxylate-21-hydroxy compounds also shown in the Phillipps et al. reference are relatively stable, this is not true of the 17-carbonate-21-hydroxy compounds. In the latter compounds, there is a tendency for migration of the carbonate group from the 17-position to the 21-position, i.e. the compounds having an hydroxy group in the 21-position are unstable. The compounds having a 21-hydroxy group which are disclosed in the present application are merely intermediates obtained in a first hydrolytic reaction. The intermediate hydroxy compounds are subsequently further reacted to esterify the 21-hydroxy group. When the 21-position is blocked in this manner, the resulting 17, 21-dicarbonates (and related compounds) then become stable.

This surprising difference in the 17- and 21-positions, which would be expected by one skilled in the art to be equivalent, is discussed in the paragraph bridging pages 6 and 7 of the specification, where the surprising aspect of the discovered

lack of equivalence is mentioned. As will be of interest to the later discussion of the Ercoli reference, attention is called to the disclosure in this same portion of the specification that a weak or dilute acid is preferably employed in the first hydrolysis step since, otherwise, the 17, 21-ortho carbonates which are the starting materials for the hydrolysis tend to hydrolyze to give 17-hydroxy-21-carbonates. These latter compounds represent the more stable materials into which the unstable compounds taught in Phillipps et al. tend to transform.

Finally, further to distinguish the claimed compounds from any compounds shown in the Phillipps et al. reference, the new claims no longer recite compounds having a β -methyl group in the 16-position.

The Examiner is further respectfully requested to reconsider his rejection of the former compound claims under 35 USC 103 as unpatentable over the teachings of Stache et al. in view of Ercoli et al.

The primary reference merely shows the 17,21-dialkyl-ortho carbonates which are the precursors of the compounds claimed. The secondary reference teaches the hydrolysis of 17,21-(1'-alkoxy)-1'-substituted methylenedioxy steroids to obtain 17-monocarboxylate esters having a hydroxy group in the 21-position. As noted above, such 17-carboxylates are stable, in contrast to the unstable 17-carbonates which tend to form the corresponding 17-hydroxy-21-carbonate compounds.

The Examiner is not correct in his assertion that "If the method shown in Ercoli were applied to the ortho esters of the primary reference, the claimed compounds would be obtained". The examples of the Ercoli patent show, for instance, the use of strong hydrochloric acid to effect hydrolysis of the starting compounds of the reference. If similarly strong acid were used to hydrolyze the ortho carbonates of Stache et al., the more stable 17-hydroxy-21-carbonate cleavage product would tend preferentially to be formed.

Even if the ortho carbonates of the primary reference were hydrolyzed, by chance, to form 17-carbonate-21-hydroxy compounds, such compounds are no longer claimed in the present application. As discussed earlier with respect to the Phillipps et al. reference, such compounds are unstable. It is a surprising and unexpected nature of the present invention that the now-claimed dicarbonate esters are, on the other hand, quite stable.

Finally, the Examiner is respectfully requested to reconsider his rejection of the method claims under 35 USC 103 for reasons variously discussed earlier herein. Thus, not only do the starting materials in the Ercoli process and the process of the present invention differ, but the use of weak acid in the present invention is critical to the formation of a 17-carbonate-21-hydroxy compound, unlike Ercoli where either weak or concentrated acid can apparently be used. Further, the claimed processes do not merely involve a hydrolysis but, also,

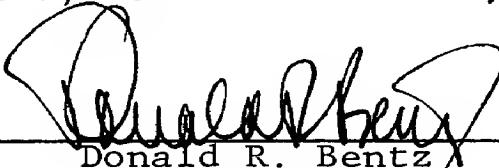
a further step in which the hydroxy group in the 21-position is altered in a manner not taught or suggested by the Ercoli et al. reference.

In view of the amendments and arguments above, favorable reconsideration of the application and passage of the application to issue with Claims 6-25 are solicited.

Respectfully submitted,

CURTIS, MORRIS & SAFFORD, P.C.

By


Donald R. Bentz

Reg. No. 18,371

DRB:jk
AC 212 840-3333